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Report

The impact of drug administration sequence and pharmacokinetic interaction in a phase I study of the combination of docetaxel and gemcitabine in patients with advanced solid tumors

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Our objective was to determine the maximum tolerated dose (MTD) of two administration sequences of docetaxel and gemcitabine in cancer patients, and to describe the pharmacokinetics of both drugs. Patients were treated in a 4-weekly schedule at two dose levels: gemcitabine 800 mg/m^2 on days 1, 8 and 15, and docetaxel 85 or 100 mg/m^2 on day 15 (levels I and II). The protocol was amended to a 3-weekly schedule, testing gemcitabine 800 or 1000 mg/m^2 on days 1 and 8, with docetaxel 85 mg/m^2 on day 8 given initially (dose levels IIIa and IV). At the recommended dose, an extra cohort of patients initially received gemcitabine (dose level IIIb). Eleven patients were treated with the 4-week schedule; 29% of cycles were delayed predominantly because of hematological toxicity. Four patients developed dose-limiting toxicities (DLTs), predominantly hematological. In the 3-week schedule, 14 patients were treated. At level IV, three of four patients developed DLTs, defining the MTD. With the reverse sequence, three patients received a total of 10 cycles. Overall, nine partial remissions were observed. We conclude the recommended dose for phase II studies is gemcitabine 800 mg/m^2 on days 1 and 8, combined with docetaxel 85 mg/m^2 on day 8, on a 3-weekly schedule. Gemcitabine distribution is significantly altered upon docetaxel administration. [© 2002 Lippincott Williams & Wilkins.]

Key words: Gemzar, Taxotere, therapeutic drug monitoring, toxicity.

Introduction

Docetaxel (Taxotere) and gemcitabine (Gemzar) exhibit significant clinical activity against several tumors. Docetaxel and gemcitabine are attractive candidates for combination therapy since they have different mechanisms of action and non-overlapping toxicities.

Docetaxel is a semisynthetic analog of paclitaxel with greater potency in promotion of microtubule assembly and inhibition of the depolymerization of tubulin. It acts as a mitotic spindle poison by blocking eukaryotic cells in the G_2/M mitotic phase of the cell cycle, resulting in the inability of the cells to divide.[1] This contrasts with the action of other spindle poisons in clinical use, such as colchicine or vinca alkaloids, which inhibit tubulin assembly in microtubules.[2] Docetaxel does not act directly on DNA; DNA damage is observed only secondarily to the activation of apoptosis.

Gemcitabine, a deoxycytidine analog, is phosphorylated to its mononucleotide by deoxycytidine kinase and subsequently by nucleotide kinases to its active metabolites, gemcitabine di- and triphosphate. The cytotoxic action of gemcitabine appears to be due to the inhibition of DNA synthesis by the di- and triphosphate nucleosides. First, gemcitabine diphosphate inhibits ribonucleotide reductase which is uniquely responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme reduces the concentrations of deoxynucleosides, in general, and that of deoxycytidine triphosphate (dCTP), in particular. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. A strong correlation exists between the extent of gemcitabine triphosphate formation, its incorporation into DNA and its inhibition of DNA synthesis. A small amount of gemcitabine may also be incorporated into RNA.

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Thus, the reduction of intracellular dCTP concentration potentiates the incorporation of gemcitabine triphosphate into DNA. DNA polymerase ε is unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into the DNA, one additional nucleotide is added to the growing DNA strands, following which there is essentially a complete inhibition of further DNA synthesis, leading to an accumulation in the G_0/G_1 and S phases, with the induction of the programmed cell death process known as apoptosis.[3,4]

The different effects of docetaxel and gemcitabine on cellular metabolism and the cell cycle, together with differences in their metabolic clearance, imply that the appropriate sequential administration of the drugs may result in the potentiation of both agents. *In vitro* studies have suggested that combining antimetabolites and taxanes in different sequences could turn antagonism into synergism and vice versa. Clinical data on the pharmacokinetic and pharmacodynamic drug–drug interactions between docetaxel and gemcitabine are limited. The objectives of this study were to determine the maximum tolerated dose (MTD) and the recommended dose for subsequent phase II studies of docetaxel and gemcitabine given in combination, and to characterize the toxicity profile. Furthermore, pharmacokinetic profiles of docetaxel and gemcitabine, when given in combination in different schedules and sequences, were studied. An additional objective of this study was to relate the pharmacokinetics of both drugs to their toxicities.

Materials and methods

Patient selection

Patients were considered eligible if they fulfilled the following criteria: (i) histologically or cytologically confirmed cancer, for which no treatment with greater potential than docetaxel or gemcitabine was available; (ii) locally advanced or metastatic disease; (iii) age $\geqslant$18 years; (iv) WHO performance status $\leqslant$2; (v) estimated life expectancy $\geqslant$12 weeks; (vi) adequate bone marrow function (absolute neutrophil count $\geqslant 2.0 \times 10^9$ cells/l, platelet count $\geqslant 100 \times 10^9$ cells/l); (vii) normal renal function [creatinine $\leqslant$ upper normal limit (UNL) or creatinine clearance $\geqslant$60 ml/min]; (viii) adequate liver function (total bilirubin $\leqslant 1 \times$ UNL, alanine transaminase (ALAT) and aspartate transaminase (ASAT) $\leqslant 2 \times$ UNL, alkaline phosphatases $\leqslant 5 \times$ UNL); (ix) no radiation therapy for at least 4 weeks (8 weeks in the case of extensive prior therapy); for the 4-week schedule, no more than *two* prior chemotherapy treatments for advanced disease, at least 4 weeks previously (6 weeks for nitrosureas, mitomycin C and carboplatin; 8 weeks if concomitant use of granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor was necessary); for the 3-week schedule, no more than *one* prior chemotherapy treatment for advanced disease, which must NOT have included mitomycin C, carboplatin or high-dose therapy; and (x) written informed consent according to institutional guidelines.

Exclusion criteria included the following: (i) hematological malignancies; (ii) symptomatic brain metastases or leptomeningeal involvement; (iii) peripheral neuropathy grade $\geqslant$2 according to NCI common toxicity criteria (CTC version 1); (iv) pre-existing ascites and/or pleural effusions; and (v) prior taxoids, gemcitabine or other nucleoside analogs.

All eligible patients who received at least one full cycle were considered evaluable for safety. Those exposed to at least two courses of treatment were considered evaluable for response to chemotherapy. Patients removed from the study on account of progressive disease, prior to completing two cycles, were also considered evaluable with an outcome of early progression.

Study design

This was a phase I study of docetaxel combined with gemcitabine in patients with advanced or metastatic solid tumors. Two treatment schedules and administration sequences were studied.

When used in a binary combination, gemcitabine is commonly administered as weekly treatment for 3 weeks followed by 1 week of rest, whilst the partner drug is usually given simultaneously either on day 1, 8 or 15. As the neutrophil nadir of docetaxel is on day 8, we anticipated that if the two compounds were to be given on day 1 or 8, it may not be possible to administer gemcitabine on day 8 or 15, respectively. Docetaxel was therefore given on day 15 in the 4-week schedule, with gemcitabine on days 1, 8 and 15. The cycles were repeated every 4 weeks in the absence of tumor progression or serious toxicities. In the 3-week schedule gemcitabine was given on days 1 and 8, with docetaxel on day 8 before gemcitabine, and the *reverse* sequence (docetaxel 1 h after

gemcitabine) was also tested at the recommended dose for phase II studies. At least four evaluable patients were scheduled at each dose level, and six at the MTD and at the recommended dose for phase II trials. If one out of four patients at one dose level developed a dose-limiting toxicity (DLT), it was planned to enter two more patients at the same dose level. A level was considered to be the MTD if at least two out of four patients or four out of six patients had experienced *the same* DLT in the first cycle. The dose level preceding the MTD was recommended as the dose for phase II trials.

Drugs

Docetaxel (provided by Aventis Pharm, Brussels, Belgium) was supplied as a Taxotere 80 mg vial containing 2 ml of a 40 mg/ml solution of docetaxel in polysorbate 80 and a Solvent for Taxotere 80 mg vial containing 6 ml of solvent. The required premix solution containing 10 mg/ml docetaxel was injected into a 250-ml infusion bag (either 5% glucose solution or 0.9% sodium chloride solution) and administered as a 1-h i.v. infusion. All patients received prophylactic premedication with oral corticosteroids for 3 days starting the evening before the docetaxel administration (dexamethasone p.o. 8 mg b.i.d. or equivalent). No further prophylactic antiemetics were given in the first cycle. In subsequent cycles, 5-HT_3 antagonists were administered if required.

Gemcitabine (Gemzar, provided by Eli-Lilly, Brussels, Belgium) was supplied as a lyophilized powder in sterile vials containing 200 or 1000 mg of gemcitabine as the hydrochloride salt, mannitol and sodium acetate. Gemcitabine was administered in 250 ml of 0.9% NaCl as a 30-min i.v. infusion, starting 1 h after the end of the docetaxel infusion.

At the end of the study a cohort of patients was treated with docetaxel given after gemcitabine, again with a 1-h interval between drug administrations.

Safety and toxicity evaluation

To evaluate clinical safety, hematology (hemoglobin, platelets, white blood cells and neutrophils), biochemistry (serum creatinine, alkaline phosphatase, ASAT, ALAT, total bilirubin, lactate dehydrogenase and γ-GT) and urinalysis were performed before study entry, weekly during therapy (twice weekly for hematology) and 4-weekly thereafter. A baseline ECG, chest X-ray and radiological assessment of tumor lesions was also performed. The ECG and chest X-ray were repeated every full cycle, with tumor evaluation every two cycles.

The toxicity for each cycle and the worst toxicity for a given patient was recorded and graded according to the National Cancer Institute CTC version 1.[5] A DLT was defined as follows: (i) febrile neutropenia; (ii) grade 4 neutropenia lasting >7 days; (iii) grade 4 thrombocytopenia; or (iv) any grade $\geqslant 3$ neurosensory, neuromotor, renal or hepatic toxicity. Hematological toxicity during the first cycle was evaluated as the percentage decrease in neutrophils, white blood cells or platelets, using the following equation: percentage decrease = (pretreatment value − value of the nadir)/pretreatment value $\times$ 100%.

Both hematological and non-hematological patient characteristics were correlated with the pharmacokinetic parameters of both gemcitabine and docetaxel by stepwise multiple linear regression: the procedures used were similar to those previously published for gemcitabine and paclitaxel pharmacokinetic and pharmacodynamic interactions.[6]

Patient data were analyzed for evidence of cumulative toxicity with repeated cycles of therapy. Dose modifications were made according to toxicity and followed a prescribed reduction to the previous dose level. In case of toxicity at the lowest dose level, appropriate dose reductions were to be discussed between the investigators and the sponsor.

Efficacy

Assessment of antitumor activity was performed every two courses and response was classified according to WHO criteria. [5–7]

Docetaxel and gemcitabine pharmacokinetics

During the first treatment cycle, blood samples for analysis of docetaxel and gemcitabine were drawn at the following time points: on day 1 s and 8 in the 4-week schedule and on day 1 in the 3-week schedule at 0 (before gemcitabine infusion), 0.5 (end of gemcitabine infusion), 1.5 and 2 h. The sampling times on day 15 in the 4-week schedule and on day 8 in the 3-week schedule were: 0 (before docetaxel

infusion), 0.5, 1 (end of docetaxel infusion), 1.5, 2, 2.5 (end of gemcitabine infusion), 3.5, 4, 8, 12, between 16 and 24, and 48 h. In the reversed sequence on day 8 in the 3-week schedule the sampling points were: 0 (before gemcitabine infusion), 0.5 (end of gemcitabine infusion), 1.5 (before docetaxel infusion), 2, 2.5 (end of docetaxel infusion), 3, 3.5, 4, 8, 12, between 16 and 24, and 48 h. Blood was collected in heparinized tubes and plasma was separated from blood cells by centrifugation (3000 *g* for 10 min at 4°C) and stored at –20°C until analysis.

Plasma concentrations of docetaxel were assayed by HPLC with a lower limit of quantitation of 5 ng/ml.[8]

The docetaxel concentration–time data were analyzed for basic parameters using non-compartmental methods: area under the concentration–time curve (AUC) extrapolated from time 0 to infinity ($AUC_{0-\infty}$), maximum drug concentration (C_{max}) and time to maximum concentration (t_{max}). Subsequently, the data were fitted to a three-compartment model, using model 19 in the WinNonlin Standard version 1.1 personal computer package (Scientific Consulting, Apex, NC). The rate constants, K_{21}, K_{31} and λ_{1-3} were determined by WinNonlin. From the computer-generated estimates, values for total clearance (Cl), volume of distribution at the steady-state (V_{SS}) and the triphasic plasma half-lives (λ_1, λ_2 and λ_3) were calculated according to standard equations. The $AUC_{0-\infty}$ was determined using the linear trapezoidal rule. The mean residence time (MRT) and area under the moment curve (AUMC) were analyzed by moment analysis.[9]

To determine gemcitabine and the inactive metabolite 2,2-difluoro-2-deoxyuridine (dFdU), 150 μl of plasma was extracted as described previously and analyzed by reverse-phase HPLC. The limit of quantitation was 10 ng/ml.

Linear regression analysis of the terminal parts of the gemcitabine plasma concentration–time curves was performed to generate elimination half-lives ($t_{1/2}\lambda_z$). AUC and Cl were calculated by non-compartmental analysis; λ_z was used to extrapolate the AUC to infinity. The MRT and V_{ss} were determined by moment analysis.

To further assess gemcitabine disposition, comparisons were made between all concentrations at 30, 90 and 120 min in all treatment groups, using the Friedmann two-way analysis of variance (ANOVA) test. An analysis of both docetaxel and gemcitabine pharmacokinetics in the various treatment groups was performed using one-way ANOVA with Scheffé's procedure for multiple comparisons. Statistical significance was determined at the 5% level.

Results

Patient characteristics

A total of 26 patients entered the study at two institutions. Patient characteristics are given in Table 1. One patient was withdrawn during the first cycle due to a grade 3 infection (remote relationship to gemcitabine) and did not receive docetaxel; the patient was not included in the analysis of the treated population. Of the 25 treated patients, 11 and 14 were treated in the 4- and 3-week schedule, respectively. One patient receiving the 4-week schedule was not eligible because of impaired renal function, and two further patients were not evaluable for response because they received fewer than two cycles and were not withdrawn due to progressive disease. In the 3-week schedule, one patient had a symptomatic neuropathy grade $\geqslant 2$ and was not eligible. It must be emphasized that for reasons of toxicity five patients did not receive the minimum planned dose on their first cycle: two patients at dose level I of the 4-week schedule, two patients at dose level I of the 3-week schedule and one patient in the reverse sequence level of the 3-week schedule. However, these patients were included in the analysis.

The following dose levels were studied: gemcitabine 800 mg/m^2 on days 1, 8 and 15 with docetaxel 85 mg/m^2 on day 15 (level I), or docetaxel 100 mg/m^2 on day 15 (level II), with cycles repeated every 4 weeks, and gemcitabine 800 mg/m^2 (level IIIa) or 1000 mg/m^2 (level IV) on days 1 and 8, with

Table 1. Patient characteristics

	4-week schedule	3-week schedule
No. entered/evaluable	11/8	14/13
Male/female	9/2	7/7
Median age [years (range)]	60 (40–69)	55 (21–75)
Median WHO PS (range)	1 (0–2)	1 (0–1)
Tumor types		
adenocarcinoma	4	2
malignant melanoma	2	1
NSCLC	2	1
squamous cell carcinoma	0	3
sarcoma	1	1
renal cell carcinoma	0	3
other	2	3
Prior therapy		
surgery only	0	2
chemotherapy	10	10
radiation therapy	3	6
hormonal therapy	1	2

docetaxel 85 mg/m^2 on day 8, with cycles repeated every 3 weeks. At the recommended dose for the 3-week schedule, the sequence of gemcitabine and docetaxel administration on the day they were both given was reversed (level IIIb).

Toxicity

Table 2 summarizes the worst hematological toxicities by dose level. The non-hematological toxicities are shown in Table 3.

A total of 34 cycles was given with the 4-week schedule: 33 cycles at level I, of which 7 cycles under the lowest initially scheduled dose per protocol, and 1 cycle at level II. Overall, six patients (55%) had at least 1 cycle delayed (29% of the cycles), three patients required a dose reduction of docetaxel and one patient a dose reduction of gemcitabine.

Using the 3-week schedule, a total of 47 cycles were given: 25 at level IIIa (docetaxel followed by gemcitabine), of which 5 cycles under the lowest initially scheduled dose, and 10 utilizing the reversed sequence at level IIIb (gemcitabine followed by docetaxel). Seven out of these 10 cycles were administered under the lowest initially scheduled dose. Twelve cycles were given at level IV, of which 6 cycles under the lowest initially scheduled dose. Overall, nine patients (64%) had at least 1 cycle delayed (40% of the cycles): five of six patients at level IIIa, two of four patients in the reversed sequence at level IIIb and two of four patients in

Table 2. Worst hematological toxicity by dose level

Dose level	No. patients	WBC		ANC		HB		PLT	
		3[a]	4	3	4	3	4	3	4
4-week schedule									
I: D85 G800	10	4	2	2	4	1	2	1	2
II: D100 G800	1	0	1	0	1	0	1	0	0
3-week schedule									
IIIa: D85 G800	6	4	2	2	4	1	0	1	1
IIIb: reversed sequence	4	5	2	3	3	2	0	0	0
IV: D85 G1000	4	1	2	0	3	0	0	1	0

[a]NCI-CTC grades 3 and 4.
WBC: white blood cells; ANC: absolute neutrophil count; HB: hemoglobin; PLT: platelets.

Table 3. Worst non-hematological toxicity

	4-week schedule			3-week schedule								
	Level I+II* $N = 11$ patients			Level III: d8: D+G $N = 6$ patients			Level III: d8: G+D $N = 4$ patients			Level IV $N = 4$ patients		
	2[a]	3	4	2	3	4	2	3	4	2	3	4
Diarrhea	1	0	0	1	0	1	0	1	0	1	1	0
Fatigue	5	1*	0	3	1	0	0	0	0	1	2	0
Febrile neutropenia	0	1	0	0	1	0	0	0	0	0	3	0
Fever	3*	1	0	2	0	0	1	1	0	3	0	0
Hypotension	0	0	1	0	0	0	0	0	0	0	0	0
Infection	0	1	1	1	1	0	1	1	0	1	0	0
Myalgia	2*	0	0	1	0	0	0	0	0	1	1	0
Nausea	1*	0	0	3	0	0	0	0	0	2	0	0
Neuropathy (sensory)	0	0	0	1	1	0	0	0	0	2	0	0
Edema	3	1*	0	1	0	0	0	0	0	1	1	0
Pulmonary	0	2	1*	0	1	0	0	0	0	1	0	0
Skin	1	1	0	2	0	0	0	0	0	2	0	0
Stomatitis	1	1	0	0	0	0	0	1	1	3	0	0
Thrombosis	0	1	0	0	0	0	0	0	0	0	1	0
Weight gain	1	0	0	0	1	0	0	0	0	0	0	0

[a]NCI-CTC grades 2–4.

level IV. Seven patients required a dose reduction of docetaxel (six at level IIIa and one at level IIIb) and eight patients a dose reduction of gemcitabine (six at level III and two at level IV).

Initially none of the patients at the 4-weekly regimen experienced DLT in the first cycle at the first dose level. For this reason, the dose was escalated as per protocol. However, the first patient at the second dose level immediately developed grade 4 hematological as well as non-hematological toxicities after the first cycle. Meanwhile, data from patients on subsequent courses at dose level I exhibited considerable toxicity, including four DLTs in cycle 2. This required dose reductions and dose delays, resulting in a considerable drop in the dose intensity achieved. Therefore, no further patients were entered at level II, but additional patients were enrolled at level I, up to a total of 10. The pattern and severity of toxicity appeared consistent, leading to the conclusion that the 4-weekly regimen was too toxic for appropriate dosing.

There was no evidence for any specific reproducible cumulative toxicity, but the decrease in dose intensity suggested overall cumulative toxicity.

According to the protocol definition of DLT, four patients at dose level I had one or more DLTs. The first patient (one of the underdosed patients) had a febrile neutropenia and grade 4 thrombocytopenia, the second patient developed grade 4 neutropenia for 8 days, the third patient had grade 4 thrombocytopenia and infection, and the fourth patient had a grade 3 infection. In addition, severe grade 3 non-hematological side effects not qualifying for DLT were seen (Table 3). Gemcitabine could be responsible for the observed pulmonary toxicity in three of these patients.

At level IIIa (docetaxel followed by gemcitabine, with docetaxel given on day 8) four of six patients experienced a DLT: a grade 3 infection (plus grade 4 diarrhea), two grade 4 neutropenias lasting >7 days, and a febrile neutropenia in combination with grade 4 thrombocytopenia and grade 3 neuropathy. However, this level was not considered the MTD, because these patients did not develop the *same* DLT. At dose level IV, three of four patients experienced the *same* DLT (febrile neutropenia), so the MTD was reached according to the protocol. In the extra cohort of patients treated at level IIIb with the reverse sequence of gemcitabine followed by docetaxel on day 8, only one patient had a DLT (grade 3 infection plus grade 4 stomatitis), as defined by protocol, but again severe grade 3 non-hematological toxicities of stomatitis and diarrhea were seen.

In both schedules, one patient experienced a thrombosis. Except for the edema and the peripheral sensory neuropathy, there was no further evidence for cumulative toxicity.

Antitumor activity

Three objective partial responses were observed in the 4-week schedule: two patients with adenocarcinoma of unknown origin (one at level II) and one with bladder cancer.

Using the 3-week schedule, six objective responses were recorded: five partial remissions, one each in patients with prostate cancer, squamous cell head and neck cancer, renal cell cancer, bladder cancer, and breast cancer, and one complete remission in a patient with ovarian cancer. Overall, there were nine objective remissions in 21 patients evaluable for response.

Docetaxel pharmacokinetics

Complete plasma sampling for docetaxel analysis was obtained in 23 patients. The shapes of the plasma concentration–time curves were comparable to those following single-agent administration in previously published reports.[10] The major estimated pharmacokinetic parameters of docetaxel for the three main groups are listed in Table 4. Groups IIIa and IV are combined, since the dose of docetaxel and sequence of drug administrations were similar. Mean clearances were comparable between the groups, and varied between 218 and 258 ml/min/m^2. The mean MRT of docetaxel ranged from 233 to 289 min and $t_{1/2}\lambda_2$ from 255 to 259 min, in accordance with data

Table 4. Estimated pharmacokinetic parameters (mean $\pm$ SD) of docetaxel groups I, IIIa+IV and IIIb

	AUC (ng/ml · min)	$t_{1/2}$ (min)	V_{ss} (l/m^2)	CL (ml/min/m^2)	MRT (min)
Group I ($n = 10$)	368245 $\pm$ 116096	355 $\pm$ 324	51.4 $\pm$ 55.3	258 $\pm$ 102	282 $\pm$ 295
Group IIIa+IV ($n = 8$)	398206 $\pm$ 154717	255 $\pm$ 461	30.5 $\pm$ 42.9	239 $\pm$ 82	233 $\pm$ 380
Group IIIb ($n = 4$)	411376 $\pm$ 116387	359 $\pm$ 384	46.5 $\pm$ 35.0	218 $\pm$ 52	289 $\pm$ 272

in the literature. Overall, no differences in docetaxel pharmacokinetics between the three groups were identified (Table 4). In group IIIb, the gemcitabine infusion started 90 min before the start of docetaxel administration. The estimated parameters of this group were not significantly different from those of groups I, IIIa and IV, and therefore an early effect of gemcitabine on docetaxel pharmacokinetics was not demonstrated. Furthermore, it can also be assumed that pretreatment with gemcitabine with a time interval of 8 days does not lead to a significant change of docetaxel pharmacokinetics.

Gemcitabine pharmacokinetics

Complete plasma sampling for gemcitabine analysis was also obtained in 23 patients. Plasma concentration–time curves of gemcitabine were generally described by a one-compartment open model. However, when gemcitabine was preceded by docetaxel, the curves were better described by a two-compartment open model. In this group $t_{1/2}\lambda_2$ was used to extrapolate to infinity and calculate MRT and V_{ss}. Mean gemcitabine concentrations 30 and 90 min after the start of the infusion were significantly decreased following docetaxel pretreatment (Figure 1, groups I+II, IIIa and IV) ($p < 0.05$) when comparisons were made between days 1, 8 and 15 (Friedmann analysis). The means $\pm$ SD of several estimated pharmacokinetic parameters of gemcitabine and its metabolite dFdU are listed in Tables 5 and 6, respectively. Groups I and II are combined, since the dose of gemcitabine and the sequence of administration were similar. The means Cl of gemcitabine was comparable to values in the literature,[11] varying from 546 to 1298 ml/min/m^2. In group IIIa, an increase in AUC from day 1 to 8 was associated with a prolongation of the $t_{1/2}\lambda_z$, which apparently counterbalanced the significant decrease in concentrations during distribution. The means $\pm$ SD of the estimated pharmacokinetic parameters of dFdU (Table 6) were similar in the treatment groups. A prolongation of $t_{1/2}\lambda_z$ was noted on the later days of the treatment cycle; differences in $t_{1/2}\lambda_z$ failed to reach the level of significance ($0.05 < p < 0.1$; one-way ANOVA over *all* groups). When comparing $t_{1/2}\lambda_z$ data in groups I+II, days 1 versus 8 and 15, a significant increase from 69 to 145 min was demonstrated ($p = 0.0005$; day 1 versus 15). The increase of $t_{1/2}\lambda_z$ between days 8 and 15 also proved to be significant (93 versus 145 min; $p = 0.01$). A parallel effect was observed with the MRT, with longer values occurring in the later days of the treatment cycle. This phenomenon was significant in groups IIIa and IV, with the MRT more than doubling on day 8 ($p < 0.05$).

Pharmacokinetics–pharmacodynamic relationships

One of the objectives of the study was to relate pharmacokinetics to pharmacodynamics. Since the side-effect profiles were similar in each group, pharmacokinetics–pharmacodynamic analyses were performed on all 23 patients evaluable for this purpose. There was no apparent relationship between pharmacokinetic parameters and either antitumor effect or toxicity in this relatively small sample.

Discussion

Docetaxel and gemcitabine are frequently used cytotoxics with activity in a range of malignancies, including non-small cell lung, breast, pancreatic, bladder and ovarian cancers. Since they have different mechanisms of action and non-overlapping toxicities, docetaxel and gemcitabine are attractive candidates for combination therapy.

Furthermore, several *in vitro* studies have shown that the activity of taxanes in combination with gemcitabine is schedule dependent. In two non-small cell lung cancer cell lines, Zoli *et al.* found that gemcitabine followed by docetaxel, after a 48-h washout period, produced only a small synergistic effect, possibly as a result of a gemcitabine induced block in the G_0/G_1 phase which only recovered after 72 h. Such a block may prevent exposure of the cells to the cytotoxic effect of docetaxel administered within this period. Conversely, when docetaxel was followed by gemcitabine, again after a 48-h washout period, a strong synergistic cytotoxic effect was observed. Docetaxel produced an initial block in the G_2/M phase, providing a large fraction of recovered synchronized cells at the G_1/S boundary, which is the specific target phase for gemcitabine.[12] Theodossiou *et al.* showed gemcitabine and paclitaxel to be antagonistic when administered simultaneously to a lung cancer cell line, with a slightly less than additive cytotoxic effect when gemcitabine administration preceded that of paclitaxel or vice versa.[13] These data suggest that giving docetaxel before gemcitabine may be more effective, but also more toxic. In the current phase I study we tried to

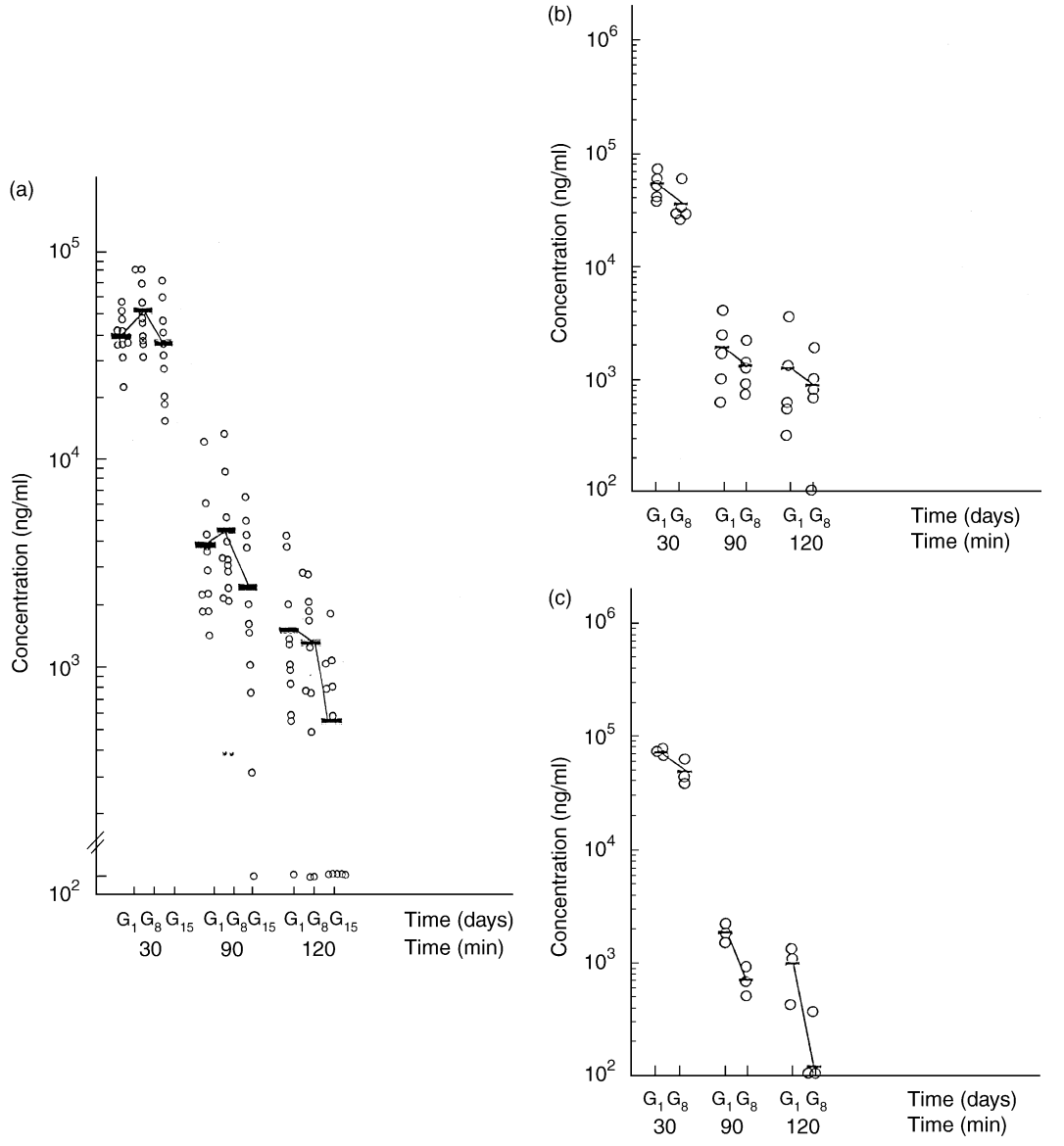

Figure 1. (A) Gemcitabine concentrations at $t = 30, 90$ and 120 min upon administration at days 1, 8 and 15 (G_1, G_8 and G_{15}, respectively). Docetaxel administration preceded gemcitabine administration with a time interval of 2 h at G_{15} (t_{inf} docetaxel = 1 h). At G_1 and G_8 gemcitabine was given solely. Dose gemcitabine = 800 mg/m^2. (B) Gemcitabine concentrations at $t = 30, 90$ and 120 min upon administration at days 1 and 8 (G_1 and G_8, respectively). Docetaxel administration preceded gemcitabine administration with a time interval of 2 h at G_8 (t_{inf} docetaxel = 1 h). At G_1 gemcitabine was given solely. Dose gemcitabine = 800 mg/m^2. (C) Gemcitabine concentrations at $t = 30, 90$ and 120 min upon administration at days 1 and 8 (G_1 and G_8, respectively). Docetaxel administration preceded gemcitabine administration with a time interval of 2 h at G_8 (t_{inf} docetaxel = 1 h). At G_1 gemcitabine was given solely. Dose gemcitabine = 1000 mg/m^2.

assess this by reversing the sequence of administration of docetaxel and gemcitabine in an extra cohort of patients treated at the recommended phase II dose. Identifying or excluding pharmacokinetic interactions between the two drugs is crucial in the presence of sequence-dependent toxicity or activity. The dose-finding trial of Rizvi,[14] with docetaxel dose levels ranging from 30 to 40 mg/m^2 and gemcitabine from 800 to 1000 mg/m^2, with both drugs administered on days 1 and 8 every 21 days, also assessed the sequence of drug administration. Toxicity appeared unaffected by drug sequence.

When combined, gemcitabine is commonly used as weekly treatment for 3 weeks followed by 1 week

Table 5. Estimated pharmacokinetic parameters (mean ± SD) of gemcitabine

	C_{max} (ng/ml)	AUC (μg/ml · min)	$t_{1/2}$ (min)	V_{SS} (l/m^2)	CL (ml/min/m^2)	MRT (min)
Group I+II						
day 1 ($n = 11$)	40472 ± 9794	1431 ± 282	29 ± 14	36.6 ± 12.3	827 ± 292	48 ± 28
day 8 ($n = 11$)	53155 ± 17503	1434 ± 608	48 ± 25	29.8 ± 10.1	650 ± 261	61 ± 40
day 15[a] ($n = 10$)	38026 ± 19711	1253 ± 668	138 ± 69	76.4 ± 65.8	806 ± 411	71 ± 23
Group IIIa						
day 1 ($n = 5$)	52215 ± 13431	1153 ± 414	112 ± 134	58.7 ± 43.3	747 ± 187	48 ± 5
day 8[a] ($n = 4$)	28808 ± 2002	1485 ± 187	561 ± 467	328.7 ± 213.4	546 ± 75	190 ± 69
Group IIIb						
day 1 ($n = 4$)	42396 ± 10620	735 ± 152	36 ± 47	45.7 ± 16.1	1121 ± 206	68 ± 54
day 8 ($n = 4$)	49824 ± 11431	439 ± 156	36 ± 21	56.9 ± 21.7	1298 ± 394	31 ± 25
Group IV						
day 1 ($n = 3$)	71823 ± 3922	1281 ± 96	42 ± 1	31.2 ± 1.6	784 ± 57	43 ± 22
day 8[a] ($n = 3$)	47689 ± 13854	812 ± 125	29 ± 5	34.2 ± 5.9	1103 ± 281	40 ± 28

[a]Docetaxel administered before gemcitabine with a 1 h interval.

Table 6. Estimated pharmacokinetic parameters (mean ± SD) of dFdU

	C_{max} (ng/ml)	AUC (μg/ml · min)	$t_{1/2}$ (min)	MRT (min)
Group I+II				
day 1 ($n = 11$)	69984 ± 15849	7207 ± 1294	69 ± 38	92 ± 41
day 8 ($n = 11$)	80853 ± 15782	8529 ± 1811	93 ± 60	126 ± 85
day 15 ($n = 10$)	62433 ± 29601	10237 ± 4215	145 ± 61	226 ± 83
Group IIIa				
day 1 ($n = 5$)	87950 ± 23211	7646 ± 2991	46 ± 22	68 ± 3
day 8 ($n = 5$)	78631 ± 8256	13808 ± 8550	299 ± 316	186 ± 79
Group IIIb				
day 1 ($n = 4$)	83630 ± 15929	10675 ± 4669	65 ± 44	150 ± 294
day 8 ($n = 4$)	78112 ± 11636	11223 ± 6821	113 ± 106	236 ± 399
Group IV				
day 1 ($n = 3$)	105780 ± 15085	9119 ± 1539	27 ± 5	70 ± 0.2
day 8 ($n = 3$)	73893 ± 21395	16732 ± 15111	253 ± 226	187 ± 29

of rest. The drug combined with gemcitabine is usually given simultaneously either on day 1, 8 or 15. As the neutrophil nadir of docetaxel is on day 8, we anticipated that in the case of administration of the two compounds on day 1 or 8, the administration of gemcitabine on day 8 or 15, respectively, would have to be delayed or stopped. As a consequence, we administered docetaxel on day 15 in this 4-week schedule. The starting dose consisted of gemcitabine 800 mg/m^2 on days 1, 8 and 15, combined with docetaxel 85 mg/m^2 on day 15 (prior to gemcitabine). This 4-week schedule was too toxic, requiring consistent gemcitabine and docetaxel dose reductions. Four of the 11 patients included in this cohort developed DLTs, consisting of neutropenia, thrombocytopenia and infection in the first cycle, and the scheduled dose intensity could not be sustained in the full cohort. Our findings are consistent with the data of Spiridonidis *et al.*,[15] who concluded that gemcitabine 800 mg/m^2 on days 1, 8 and 15 can be safely combined with docetaxel 100 mg/m^2 on day 1 of a 28-day cycle, but not with docetaxel on day 15.

Despite the frequent dose reductions and necessary cycle delays in this 4-week schedule, three of 11 patients had an objective tumor response. Therefore, the protocol was amended to a 3-week schedule, with gemcitabine on days 1 and 8, combined with docetaxel on day 8. At dose level IIIa, gemcitabine 800 mg/m^2 and docetaxel 85 mg/m^2, four of six treated patients developed DLTs consisting of infection, neutropenia, thrombocytopenia and neuropathy, but only two in the first cycle. Nevertheless, according to protocol definition, this level was not considered as the MTD, since these patients did not develop the *same* DLT. We believe that in retrospect this proves that requiring the *same* DLT for assess-

ment of MTD is inappropriate. Taxanes, and many other cytotoxic drugs, can produce different DLTs, all of which should be taken into account in the decision-making process. Certainly, in the case of combination regimen phase I trials, it may be worthwhile specifying a certain minimum dose intensity for further studies.

The MTD was formally reached at level IV, gemcitabine 1000 mg/m^2 and docetaxel 85 mg/m^2, since three of the four treated patients experienced febrile neutropenia. As initially planned, the sequence of administration of docetaxel and gemcitabine on day 8 was reversed (gemcitabine before docetaxel), in an extra cohort at the recommended phase II dose (dose level III). Only one patient in this cohort developed DLT, a grade 4 infection. However, two others experienced severe stomatitis, one in combination with diarrhea; both had been irradiated previously in the involved area (mouth and rectum). Reversing the sequence of administration of docetaxel and gemcitabine on day 8 does not seem to influence the toxicity of this combination, confirming the results of Rizvi.[14]

Overall the 3-week schedule was not easier to administer in terms of planned dose intensity, and most patients had at least one cycle delayed and required a dose reduction. Nevertheless, the combination of docetaxel and gemcitabine showed interesting antitumor activity. Other phase I trials using a similar schedule, with day 1 and 8 gemcitabine and day 8 docetaxel, have been reported as abstracts, with recommended doses of docetaxel/gemcitabine for phase II trials of 90/1000 or 75/1250, 85/1000 and 85/800 mg/m^2.[16–18] Rischin *et al.*[19] advised a dose of 1200 mg/m^2 gemcitabine and 85 mg/m^2 docetaxel with prophylactic ciprofloxacin. A mixture of prior chemotherapy regimens, together with differences in the criteria used to determine the recommended dose, may have contributed to the variability in these dose levels.

Our study is unique in investigating the pharmacokinetics of both agents. Docetaxel pharmacokinetics were consistent with single agent data reported in the literature,[20,21] indicating a lack of interference by gemcitabine. In contrast, gemcitabine pharmacokinetics were found to be changed significantly by co-administration of docetaxel. Since the self-induction of gemcitabine clearance could be excluded (Tables 5 and 6), it appears that docetaxel significantly alters gemcitabine distribution. Furthermore, gemcitabine elimination tended to be protracted after the distribution phase. Conversely, $t_{1/2}\lambda_z$ in group IV at day 8 was shorter than $t_{1/2}\lambda_z$ at day 1; this difference, however, was found only in a small group of patients ($n = 3$) and will thus require further assessment to confirm its significance. The change in gemcitabine distribution after docetaxel pretreatment may be caused by the partitioning of gemcitabine between the different blood constituents of cells, plasma and plasma water. This will be the subject of further studies, using techniques for the analysis of blood sediments.[22] There was no clear pharmacokinetic–pharmacodynamic (toxicity) relationship for docetaxel or gemcitabine. This contrasts with a previous study combining paclitaxel and gemcitabine, where gemcitabine C_{max} was related to thrombocytopenia.[6] Changes in dFdU pharmacokinetics following docetaxel treatment were identified, similar to those observed with gemcitabine, but are less likely to have clinical impact since dFdU lacks activity.

Conclusion

The combination of gemcitabine and docetaxel, with docetaxel given on day 8 or 15, caused predominantly hematological toxicity, and was difficult to administer. The significant pharmacokinetic interaction observed does not seem to have a clinical impact. Despite its toxicity, the combination seems to be quite active and thus merits further investigation in a less pretreated patient population. The recommended dose for phase II studies is gemcitabine 800 mg/m^2 on days 1 and 8, combined with docetaxel 85 mg/m^2 on day 8, given in a 3-weekly schedule.

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